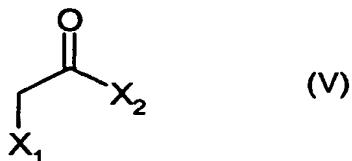


Claims:

1. Process for the preparation of a N-(N'-substituted glycyl)-2-cyanopyrrolidine comprising at least

(a) reacting, in the presence of dimethylformamide, a compound of formula (V)



wherein, independently of each other, X₁ and X₃ are halogen; X₂ is halogen, OH, O-C(=O)-CH₂X₃, -O-SO₂-(C₁₋₈)alkyl or -O-SO₂-(aryl),

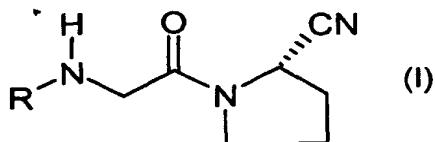
with L-prolinamide, followed by

(b) reacting the resultant compound without isolation with a dehydration agent, optionally followed by

(c) reacting, in the presence of a base, the resultant compound without isolation with an appropriate amine and

(d) recovering the resultant compound in free form or in acid addition salt form.

2. A process according to claim 1 wherein the N-(N'-substituted glycyl)-2-cyanopyrrolidine is a compound of formula (I)



wherein R is

a) R₁R_{1a}N(CH₂)_m - wherein

R₁ is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy or halogen;

R_{1a} is hydrogen or (C₁₋₈)alkyl; and

m is 2 or 3;

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b) $(C_{3-12})\text{cycloalkyl}$ optionally monosubstituted in the 1-position with $(C_{1-3})\text{hydroxyalkyl}$;

c) $R_2(\text{CH}_2)_n$ - wherein either

R_2 is phenyl optionally mono- or independently di- or independently trisubstituted with $(C_{1-4})\text{alkyl}$, $(C_{1-4})\text{alkoxy}$, halogen or phenylthio optionally monosubstituted in the phenyl ring with hydroxymethyl; or is $(C_{1-8})\text{alkyl}$; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with $(C_{1-8})\text{alkyl}$; a pyridinyl or naphthyl moiety optionally mono- or independently disubstituted with $(C_{1-4})\text{alkyl}$, $(C_{1-4})\text{alkoxy}$ or halogen; cyclohexenyl; or optionally substituted adamanyl; and

n is 1 to 3; or

R_2 is phenoxy optionally mono- or independently disubstituted with $(C_{1-4})\text{alkyl}$, $(C_{1-4})\text{alkoxy}$ or halogen; and

n is 2 or 3;

d) $(R_3)_2\text{CH}(\text{CH}_2)_2$ - wherein each R_3 independently is phenyl optionally mono- or independently disubstituted with $(C_{1-4})\text{alkyl}$, $(C_{1-4})\text{alkoxy}$ or halogen;

e) $R_4(\text{CH}_2)_p$ - wherein R_4 is 2-oxopyrrolidinyl or $(C_{2-4})\text{alkoxy}$ and p is 2 to 4;

f) isopropyl optionally monosubstituted in 1-position with $(C_{1-3})\text{hydroxyalkyl}$; or

g) R_5 wherein R_5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or multi-substituted with $(C_{1-8})\text{alkyl}$; adamanyl; substituted adamanyl; or $(C_{1-8})\text{alkyl}$ optionally mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl optionally mono- or independently disubstituted with $(C_{1-4})\text{alkyl}$, $(C_{1-4})\text{alkoxy}$ or halogen; in free form or in acid addition salt form.

3. A process according to claim 1 or 2 wherein the dehydration agent of step (b) is a (haloalkylene)dialkylammonium halogenid.

4. A process according to claim 1 or 2 wherein the dehydration agent of step (b) is (chloromethylene)dimethylammonium chloride.

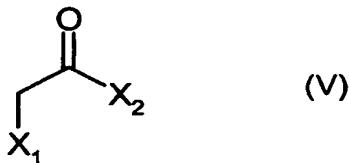
5. A process according to claim 2 wherein the amine of step (c) is a compound of formula (VI)



wherein R is as defined for formula (I) in claim 2.

6. A process according to claim 2 comprising

(a) reacting, in the presence of dimethylformamide, a compound of formula (V)



wherein X_1 is halogen; X_2 is halogen, OH, O-C(=O)-CH₂X, -O-SO₂-(C₁₋₈)alkyl or -O-SO₂-(aryl), with L-prolinamide, followed by

(b) reacting the resultant compound without isolation with

(chloromethylene)dimethylammonium chloride, followed by

(c) reacting, in the presence of a base, the resultant compound without isolation with a compound of formula (VI)



wherein R is as defined for formula (I) and

(d) recovering the resultant compound in free form or in acid addition salt form.

7. A process according to claim 6 wherein R is R₂(CH₂)_n- and R₂ is substituted adamantyl; and n is 0, 1, 2 or 3.

8. A composition of N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine, obtainable according to the process of claim 1 or 2, whereby 95% to 99,9% is N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and 5% to 0,1% is N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine, especially whereby 98% to 99,99% is N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and 2% to 0,01% is N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine.

9. A composition comprising a N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and a N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine, whereby 98% to 99,9% is N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and 2% to 0,1% is N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine, preferably whereby 98% to 99,99% is N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and 2% to 0,01% is N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine, most preferably whereby 99% to 99,99% is N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and 1% to 0,01% is N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine.

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10. A composition of N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine and N-(N'-substituted glycyl)-2(R)-cyanopyrrolidine, obtainable according to the process of claim 1 or 2.

11. A pharmaceutical composition comprising,

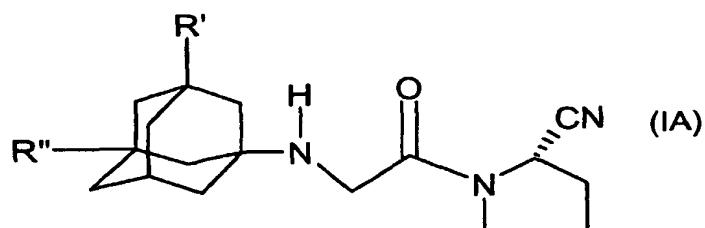
- a) one or more pharmaceutically acceptable excipients, and
- b) at least one N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine obtainable according to the process of claim 1 or 2.

12. A pharmaceutical composition comprising,

- a) one or more pharmaceutically acceptable excipients, and
- b) at least one N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine, and
- c) between 0.00001% and 5% by weight of at least one (haloalkylene)dialkylammonium halogenid.

13. A composition according to claim 12, wherein the N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine is obtainable according to the process of claim 1 or 2.

14. A composition according to any of claim 8 to 13, whereby the N-(N'-substituted glycyl)-2(S)-cyanopyrrolidine is a compound of the formula



wherein R' is hydroxy and R'' is hydrogen in free form or in acid addition salt form.